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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,029	05/19/2006	Yukako Fukuhira	Q95047	7517

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,029	FUKUHIRA ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6 and 8-16* is/are pending in the application.

4a) Of the above claim(s) *5,11 and 13-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6,8-10,12 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/23/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment and submission filed on July 23, 2009 that includes a response to the Advisory action dated June 30, 2009, has been entered. Claim 6 has been amended, and claims 12-16 newly added. No claims were cancelled. Accordingly, claims 1, 3-6 and 8-16 are pending in the Application. Claims 5 and 11 stand withdrawn from further consideration, without traverse, as drawn to non-elected inventions. The claims have been examined commensurate in scope with the elected invention, and the species of the invention, i.e. polylactic acid and phosphatidylethanolamine. Thus, new claims 13-15 have additionally been withdrawn as directed to non-elected polymers.

Claims 1, 3, 4, 6, 8-10, 12 and 16 are under current examination.

Information Disclosure Statement

The information disclosure statement filed June 23, 2009 fails to comply with 37 CFR 1.98(a)(3)(ii), which requires a copy of the translation if a written English-language translation of a non-English-language document, or portion thereof, is within the possession, custody, or control of, or is readily available to any individual designated in § 1.56(c). It has been placed in the application file, but the information referred to therein has not been fully considered, since the publication by Sato et al. is in the Japanese language.

Withdrawn Claim Objection

Claim 6 was objected to for minor informalities, in the Office action dated March 23, 2009. Applicants' amendment of the claim to delete the word "compound" obviates the ground for objection. Thus, the objection is hereby withdrawn.

Withdrawn Claim Rejections - 35 USC § 103

Claims 1-4 and 8-10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Nishikawa et al. (Materials Sci. and Eng. C8-9: 495-500; 1999), in view of Watanabe et al. (Biomacromolecules 3:1109- 1114; 2002), and further in view of Sawhney, A. (U.S. Patent No.: 6,818,018; filed Aug. 14, 1998); and claims 1 and 6 were rejected under 35 U.S.C. §103(a) as being unpatentable over Nishikawa et al. (Materials Sci. and Eng. C8-9: 495-500; 1999), in view of Watanabe et al. (Biomacromolecules 3:1109- 1114; 2002), and further in view of Sawhney, A. (U.S. Patent No.: 6,818,018; filed Aug. 14, 1998), as applied to claims 1-4 and 8-10 above, and further in view of Zou et al. (U.S. Patent Publication No.: 2002/0187105; filed Feb. 1, 2002), in the previous Office action dated March 23, 2009.

Applicants have correctly indicated that polylactic acid does not constitute an amphiphilic polymer, as required by Nishikawa et al. and therefore a person of ordinary skill would not have combined the teachings of Watanabe et al. directed to a phospholipid co-polymer of poly (lactic acid) with that of Nishikawa et al. Thus, upon further consideration the previous rejections are hereby withdrawn.

The claims are however subject to new rejections over the prior art as indicated below.

New Claim Rejections - 35 USC § 103

Claims 1, 3, 4, 8-10 and 12 are newly rejected under 35 U.S.C. §103(a) as being unpatentable over Nishikawa et al. (Mat. Res. Soc. Symp. Proc. 724:N11.7.1-N11.7.6; 2002), in view of Watanabe et al. (Biomacromolecules 3:1109- 1114; 2002), and further in view of Sawhney, A. (U.S. Patent No.: 6,818,018; filed Aug. 14, 1998).

The claims embrace a tissue regeneration substrate comprising a film with a honeycomb

structure having an average cavity inner diameter from 0.1 to 20 μm, composed primarily of polylactic acid polymer and phosphatidylethanolamine.

Nishikawa et al. describe honeycomb microporous films comprising biodegradable polymers that include poly (L-lactic acid) and an amphiphilic polymer, for tissue engineering (Title and Abstract). The preparation of honeycomb films for cell culture substrates is described under Experimental details, p. N11.7.1. The authors state that the honeycomb film was prepared by applying moist air to spread polymer solution on surface of water microspheres that are prevented from fusing by the surfactant effect of the amphiphilic polymer (p. N11.7.3). Nishikawa et al. depict the self-supporting honeycomb film of polylactic acid n Figure 2(a), that appear to have an average diameter of about 2-3 μm (limitation of claims 1 and 12).

While Nishikawa et al. do not describe including a phospholipid in their polymer film, phosphilipids as surfactants were common knowledge, and the use of phospholipid polymers for tissue engineering was well known in the prior art, as described by Watanabe et al., teaching a porous scaffold as a cell-compatible material composed of a phospholipid co-polymer of poly (lactic acid) for tissue engineering (Title and Abstract). Thus, curing the deficiency of a phospholipid in Nishikawa et al., and providing the motivation to include phospholipid polymers in constructing honeycomb structured films as tissue substrates. As the disclosure of both Nishikawa et al. and Watanabe et al. are directed to porous tissue regeneration substrates, it would have been obvious to include the phospholipid described by Watanabe et al. in the co-polymer film of Nishikawa et al. (limitation of claim 9).

The phospholipid described in constructing the porous scaffold of Watanabe et al. is MPC, and not phosphatidylethanolamine. Sawhney et al. describe polymerizable hydrogels as matrices for carrying cells (Title and Abstract), comprising various polymers and lipids such as phosphatidylethanolamine (lines 35-36, column 12; limitation of claims 1, 3, 4 and 12), that are further biodegradable (line 21, column 13; limitation of claim 2). Thus, curing the deficiency of phosphatidylethanolamine in Nishikawa et al. and Watanabe et al., and providing the motivation to include phosphatidylethanolamine as a phospholipid in their porous tissue regeneration complex. Sawhney et al. further describe using the hydrogel for tissue augmentation or implant for cartilage (lines 22-29, column 19; limitation of claims 8 and 10).

The teachings of Nishikawa et al., Watanabe et al. and Sawhney are all directed to polymeric scaffolds and complexes for tissue regeneration. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine their respective teachings to include phosphatidylethanolamine as a phospholipid in the honeycomb film cell substrate with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would be motivated to augment the honeycomb film of Nishikawa et al. with a phospholipid, because phospholipids were known to act as surfactants and were additionally taught by Watanabe et al. as a co-polymer constituent, and such would provide a superior cell compatible phospholipid copolymer, that coupled with the biodegradable properties described by Sawhney, would produce a complex suitable for cell delivery and tissue regeneration.

Claims 1, 6 and 16 are newly rejected under 35 U.S.C. §103(a) as being unpatentable over Nishikawa et al. (Mat. Res. Soc. Symp. Proc. 724:N11.7.1-N11.7.6; 2002), in view of Watanabe et al. (Biomacromolecules 3:1109- 1114; 2002), and further in view of Sawhney, A. (U.S. Patent No.: 6,818,018; filed Aug. 14, 1998), as applied to claims 1, 3, 4, 8-10 and 12 above, and further in view of Zou et al. (U.S. Patent Publication No.: 2002/0187105; filed Feb. 1, 2002).

The claims embrace a tissue regeneration substrate comprising a film with a honeycomb structure having an average cavity inner diameter from 0.1 to 20 μm, composed primarily of a polymer compound and phosphatidylethanolamine, characterized in that the compositional ratio of the polymer compound and the phospholipid is 10:1 to 500:1 and 50:1 to 200:1 by weight.

Nishikawa et al. describe honeycomb-patterned films of amphiphilic and polylactic acid co- polymers as cell culture substrates, (Title and Abstract), having an average diameter of about 2-3 μm diameter (Figure 2(a).

While Nishikawa et al. do not describe including a phospholipid to their polymer film, the use of phospholipid polymers for tissue engineering is described by Watanabe et al., teaching a porous scaffold as a cell-compatible material composed of a phospholipid co-polymer of poly (lactic acid) for tissue engineering (Title and Abstract). Thus, curing the deficiency of a

phospholipid in Nishikawa et al., and providing the motivation to include phospholipid polymers in constructing honeycomb structured films as tissue substrates.

Sawhney et al. describe polymerizable hydrogels as matrices for carrying cells (Title and Abstract), comprising various polymers and lipids such as phosphatidylethanolamine (lines 35-36, column 12; limitation of claim 1), that are further biodegradable (line 21, column 13). Thus, curing the deficiency of phosphatidylethanolamine in Nishikawa et al. and Watanabe et al., and providing the motivation to include phosphatidylethanolamine as a phospholipid in their porous tissue regeneration complex.

Zou et al. describe polymeric combinations for delivery of therapeutically effective compositions (Title and Abstract), that include lipids, such as phosphatidylethanolamine (¶ [0124], p. 11), and wherein the ratio of lipid to polymer is the composition is from about 1:2 to 1:20 (i.e. equivalent to a 2:1 to 20:1 polymer to lipid ratio; meeting the limitation of claim 6).

While Watanabe et al. and Sawhney et al. do not specify a compositional ratio of the polymer compound and the phospholipid as 50:1 to 200:1 by weight (claim 16), the non-criticality of the claimed range is also evident by the fifty fold weight ratio difference instantly claimed, and the teachings of the instant specification, that include a 1000 fold weight ratio in a preferred embodiment, and further state: "the source of the phospholipid composing the film of the invention is not important, and the phospholipid may be one extracted from animal tissue or one produced by artificial synthesis." (pp. 5 and 6). Applicants should further note that as indicated in MPEP 2144.05: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

The teachings of Nishikawa et al., Watanabe et al., Sawhney and Zou et al. are all directed to polymeric scaffolds and complexes. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine their respective teachings to include

phosphatidylethanolamine as a phospholipid in the honeycomb film cell polymeric substrate in any desired lipid to polymer ratio with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would be motivated to augment the honeycomb film of Nishikawa et al. with a phospholipid, and would employ a given lipid to polymer ratio as a matter of design choice, because such would provide a superior cell compatible phospholipid copolymer, that coupled with the biodegradable properties described by Sawhney, would produce a complex suitable for cell delivery and tissue regeneration.

Response to Arguments

To the extent that Applicants' arguments may apply to the new rejections set forth above, they are addressed as follows:

As an initial matter it should be noted that contrary to Applicants' arguments, the instant claims do not exclude the presence of amphiphilic polymers in the tissue regeneration substrate. Base claim 1 is directed to a substrate comprising primarily of one or more polymers of polylactic acid, and a phospholipid. Thus, while the substrate polymer is primarily polylactic acid, it may include additional elements such as amphiphilic polymers.

Applicants argue that Zou et al discloses in paragraph [0024] that the ratio of the cationic lipid to the polycationic polymer in the composition is from about 1:2 to 1:20 which does not teach, suggest or otherwise render obvious the 50:1 to 200:1 compositional ratio range recited in new claim 16. Applicants, arguments have been fully considered, but are not found persuasive.

As previously indicated on page 6 of the Office action dated April 2, 2008, altering the concentration of subject matter encompassed by the prior art will not support patentability, unless there is evidence that such concentration is critical. The non-criticality of the ratio is evident by the 10:1 to 500:1 and 50:1 to 200:1 ratios of polymer to phospholipid claimed.

Withdrawn Obviousness Type Double Patenting

Claims 1, 3, 4 and 6 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4-10 and 12 of copending

U.S. Patent Application No.: 10/552,685 (Patent Publication No.: 2006/0189911; commonly assigned), in the previous Office actions dated April 2, 2008 and March 23, 2009.

Applicants have filed a terminal disclaimer, rendering the rejection moot. Thus, the rejection is hereby withdrawn.

Conclusion

Claims 1, 3, 4, 6, 8-10, 12, and 16 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Primary Examiner, Art Unit 1633